

## REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

### I. Status of the Claims

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, are presented, with an appropriate defined status identifier.

Claims 10-27, 41, and 46 have been cancelled, without prejudice or disclaimer thereof. Applicants reserve the right to prosecute the subject matter of the cancelled claims in this or another application.

In addition, claims 28, 39, and 40 have been amended to state that the liquid of the aerosol is aqueous or water. Exemplary support for this amendment can be found in the specification at, for example, page 2, lines 25-26 ("there is provided an aerosol comprising droplets of an aqueous dispersion of nanoparticles . . ."). Claim 28 has also been amended to clearly recite the method steps disclosed at page 2, line 35, through page 3, line 5, of the application, and to recite that the particle size of the active agent is reduced to a "submicron" size. Exemplary support for this claim limitation can be found in the specification at, for example, page 13, lines 14-15 ("In a particularly preferred method, a therapeutic or diagnostic agent is prepared in the form of submicron particles . . .").

Claims 47-59 have been added to the application. These claims further define the particle size of the active agent of claim 28. Exemplary support for the new claims given in the application is provided in the following table.

| New Claim(s) | Exemplary Support in the Application   |
|--------------|--|
| 47           | Page 10, lines 14-25 ("The coarse therapeutic or diagnostic agent selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. . . .The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 1000 nm.") |
| 48           | Page 16, lines 24-27 ("By 'an effective average particle size of less than about 1000 nm' it is meant that at least 90% of the particles have a weight average particle size of less than about  |

| New Claim(s)   | Exemplary Support in the Application  |
|----------------|---|
|                | 1000 nm . . . )   |
| 49, 50         | Page 16, lines 24-33 (“By ‘an effective average particle size of less than about 1000 nm’ it is meant that at least 90% of the particles have a weight average particle size of less than about 1000 nm . . . With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average . . .”) |
| 51, 54         | Page 16, lines 24-29 (“By ‘an effective average particle size of less than about 1000 nm’ it is meant that at least 90% of the particles have a weight average particle size of less than about 1000 nm . . . In preferred embodiments, the effective average particle size is less than about 400 nm and more preferably less than about 300 nm . . .”)  |
| 52, 53, 55, 56 | Page 16, lines 27-33 (“In preferred embodiments, the effective average particle size is less than about 400 nm and more preferably less than about 300 nm . . . With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average . . .”)   |
| 57             | Page 16, lines 24-30 (“By ‘an effective average particle size of less than about 1000 nm’ it is meant that at least 90% of the particles have a weight average particle size of less than about 1000 nm . . . In some embodiments, an effective average particle size of less than about 100 nm has been achieved”.)  |
| 58, 59         | Page 16, lines 29-33 (“In some embodiments, an effective average particle size of less than about 100 nm has been achieved”. . . . With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size less than the effective average . . .”)  |

As the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

Following entry of this Amendment, claims 28-40, 42-45, and 47-59 are pending.

## **II. Summary of the Claimed Invention**

The claimed invention is directed to a method of delivering to the lungs of a mammal an aerosol formulation of a poorly soluble nanoparticulate therapeutic agent. The claimed invention utilizes nanoparticulate active agent particles having a submicron particle size and having one or more surface stabilizers adsorbed to the surface of the active agent particles.

The stabilized nanoparticulate active agent particles are dispersed in a liquid continuous phase, such as water. This type of formulation is known as a colloidal dispersion. In the claimed invention, the liquid dispersions are aerosolized to produce fine (i.e., less than 50  $\mu\text{m}$  diameter) liquid droplets of the colloidal dispersion.

Prior to the present invention, nanoparticulate formulations were known. *See e.g.*, U.S. Pat. No. 5,145,684, cited by the Examiner. However, it was not known that such nanoparticulate formulations could be incorporated into aerosol formulations, much less any that could be delivered to a mammal's lung as discovered and claimed by the present invention.

The claimed invention satisfies a need in the art for aerosol compositions that can deliver a poorly soluble active agent to the lungs, a need which is not met by prior disclosures. Moreover, the claimed invention is not described or suggested in the cited prior art.

## **III. The Office Action**

### **A. Withdrawal of the Rejection of Claim 28 Under 35 U.S.C. § 112, Second Paragraph**

Applicants acknowledge the Examiner's withdrawal of the rejection of claim 28 under 35 U.S.C. § 112, second paragraph.

### **B. Rejection of Claims 28-45 Under 35 U.S.C. § 112, First Paragraph**

Claims 28 – 45 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite on two grounds. First, the claim limitation "liquid droplet" allegedly lacks support in the specification. Second, the method steps of claim 28 are allegedly not

disclosed. Office Action at pages 2-3. Applicants respectfully traverse this ground for rejection.

### 1. Rejection of Claim 28 for the Recitation of “Liquid Droplet”

While Applicants respectfully disagree with this ground of rejection, claim 28 has been amended to recite “aqueous” droplets for the sole purpose of advancing the prosecution of this case. This ground for rejection is now moot.

### 2. Rejection of Claim 28 for Alleged Lack of Support for the Method Steps

Continuing, the Examiner rejected claim 28 as “the *steps* of the method as claimed in claim 28 are not disclosed.” Office Action at page 3 (emphasis in original).

While Applicants respectfully disagree with this ground for rejection, claim 28 has been amended to clearly recite method steps as taught at page 2, line 35, through page 3, line 5, of the application. For the convenience of the Examiner, shown in the chart below is a comparison of the language recited in claim 28 and exemplary supporting language recited in the application.

| Claim 28  | Exemplary Support in the Application   |
|---|--|
| 28. A method of delivering an aerosol to the lungs of a mammal comprising the steps of:   | “In yet another aspect of the invention, there is provided a method of treating a mammal comprising the steps of: . . . b) administering said aerosol to the respiratory system of said mammal.” (Page 2, line 35, through page 3, line 5) |
| (a) providing an aerosol composition, wherein said composition comprises aqueous droplets | “there is provided a method of treating a mammal comprising the steps of:<br>a) forming an aerosol of an aqueous dispersion . . .” (Page 2, line 35, through page 3, line 1.)  |
| having a particle size of less than about fifty microns in diameter,                      | “The droplets in the aerosols typically have a size less than about 50 microns in diameter . . .” (Page 3, lines 18-19.)   |
| wherein the aqueous droplets comprise:<br>(i) water,                                      | “there is provided a method of treating a mammal comprising the steps of:<br>a) forming an aerosol of an aqueous dispersion of nanoparticles,  |
| (ii) crystalline particles of a   | “there is provided a method of treating a  |

| Claim 28  | Exemplary Support in the Application   |
|---|--|
| therapeutic agent   | <p>mammal comprising the steps of:</p> <p>a) forming an aerosol of an aqueous dispersion of nanoparticles, said nanoparticles comprising insoluble therapeutic agent particles . . .” (Page 2, line 35, through page 3, line 2.)</p> <p>“The therapeutic or diagnostic agent exists as a discrete, crystalline phase.” (Page 4, lines 11-12.)</p>  |
| which is poorly soluble in water,   | <p>“The therapeutic or diagnostic agent must be poorly soluble and dispersible in at least one liquid medium. . . A preferred liquid dispersion medium is water.” (Page 4, lines 17-21.)</p>   |
| wherein the crystalline particles have a submicron particle size; and   | <p>In a particularly preferred method, a therapeutic or diagnostic agent is prepared in the form of submicron particles . . . (Page 13, lines 14-15.)</p> <p>“The coarse therapeutic or diagnostic agent selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. . . The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 1000 nm.” (Page 10, lines 14-25.)</p> <p>“As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art . . . By "an effective average particle size of less than about 1000 nm . . . (Page 16, lines 19-25.)</p> |
| (iii) at least one surface modifier adsorbed on the surface of the crystalline therapeutic agent particles; and | <p>having a surface modifier on the surface thereof;</p> <p>(Page 3, line 3.)</p>  |
| (b) administering said aerosol composition to the respiratory system of said mammal.                            | <p>b) administering said aerosol to the respiratory system of said mammal.</p> <p>(Page 3, lines 4-5.)</p>   |

As claim 28 is fully supported by the application, withdrawal of this ground for rejection is respectfully requested.

**C. Rejection of Claims 28-45 Under 35 U.S.C. § 103(a)**

**1. Wiedmann and Liversidge**

Claims 28-45 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,747,001 to Wiedmann et al. (“Wiedmann”) and U.S. Patent No. 5,145,684 to Liversidge et al. (“Liversidge”). Office Action at page 3. Applicants respectfully traverse this ground for rejection.

**a. Wiedmann is not Available as Prior Art Against the Presently Claimed Invention**

In Applicants’ previous response, filed on December 2, 2002, Applicants argued that Wiedmann is not available as prior art because Applicants claim priority as of February 24, 1995, while Wiedmann was filed on February 25, 1995 and issued on May 5, 1998. In response to Applicants’ arguments, the Examiner stated that:

The filing date of the parent application cannot be granted, as the subject matter as presently claimed was not found.

Office Action at page 3. Applicants respectfully disagree with the Examiner’s conclusion.

In particular, the Examiner noted that she could not find support for “a liquid” and particles having an average size of less than about 1000 nm. The first issue is now moot, as the claims as amended do not recite a liquid; rather, they recite either water or an aqueous dispersion, which is supported by the priority document. *See e.g.* page 3, lines 16-18 (“there is provided an aerosol comprising an aqueous dispersion of nanoparticles . . .”)

While Applicants respectfully disagree with the Examiner regarding the second issue of alleged lack of support, claim 28 has been amended to recite “submicron” particles. This term is clearly supported in the priority document. *See e.g.*, page 17, line 35, through page 18, line 1, of USSN 08/394,103, filed on February 24, 1995 (““In a particularly preferred

method, a therapeutic or diagnostic agent is prepared in the form of submicron particles . . .”). Accordingly, this ground for rejection is moot, and Wiedmann et al. is therefore not available as prior art against the claimed invention.

**b. Liversidge does not Teach or Suggest Aerosol Compositions of Nanoparticulate Active Agents**

Liversidge is directed to nanoparticulate active agent compositions, comprising a nanoparticulate active agent having a particle size of less than about 400 nm, and a surface stabilizer adsorbed onto the surface of the active agent. *See* Liversidge at col. 2, lines 38 – 43. Liversidge, however, does not teach or suggest aerosol compositions of nanoparticulate active agents or methods of administering the same. Therefore, because Wiedmann is not available as prior art and Liversidge does not teach or suggest the claimed invention, it would not have been obvious to one of ordinary skill in the art to arrive at the claimed invention given the cited references.

Moreover, one of ordinary skill in the art at the time the claimed invention was made would not have been motivated to make an aerosol composition comprising the nanoparticulate active agent composition of Liversidge for the reasons provided in Applicants’ response of December 2, 2002.

**2. Wiedmann**

Claims 28-45 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,747,001 to Wiedmann et al. (“Wiedmann”). Office Action at pages 7-8. Applicants respectfully traverse this ground for rejection.

As noted above, Wiedmann is not available as prior art against the claimed invention. Withdrawal of this ground for rejection is respectfully requested.

**3. Wiedmann, Wood, and Liversidge**

Claims 28-45 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,747,001 to Wiedmann et al. (“Wiedmann”), U.S. Patent No. 6,264,922

to Wood et al. (“Wood”), and U.S. Patent No. 5,145,684 to Liversidge et al. (“Liversidge”). Office Action at pages 10-12. Applicants respectfully traverse this ground for rejection.

As noted above, Wiedmann is not available as prior art against the claimed invention. In addition, Wood, having a priority date of February 25, 1995 and an issue date of July 24, 2001, is not available as prior art against the claimed invention. Finally, Liversidge alone does not teach or suggest the claimed invention, as discussed above and at length at pages 7-9 of Applicants’ Amendment filed on December 2, 2002. Accordingly, withdrawal of this ground for rejection is respectfully requested.

**D. Obviousness-Type Double Patenting Rejection  
Over U.S. Patent Nos. 6,264,922 and 5,747,001**

Claims 28 – 45 are rejected as being allegedly obvious over claims 24 – 30 of U.S. Patent No. 6,264,922 in the context of nonstatutory double patenting. Office Action at page 7.

In addition, claims 28 – 45 are rejected as being allegedly obvious over claims 1-10 of U.S. Patent No. 5,747,001 in the context of nonstatutory double patenting. Office Action at page 7.

While Applicants respectfully disagree with these grounds for rejection, filed herewith for the sole purpose of advancing the prosecution of this case are Terminal Disclaimers for U.S. Patent Nos. 6,264,922 and 5,747,001.

IV. CONCLUSION

Applicants courteously request reconsideration of this application in view of the amendments and foregoing remarks. Applicants submit that this application is now in condition for allowance and an early notice to that effect is respectfully solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date Feb 4, 2004

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If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.